REMARKS

In response to the final Office Action mailed September 2, 2009, in connection with the above-identified application, Applicants respectfully request entry of the following remarks. Claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are pending and under consideration.

Regarding the Claim Amendments

The claims have been amended to address informalities. In particular, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 have been amended to substitute the term "functional" with the term "antigen-binding" solely in order to advance prosecution and without acquiescing to the Examiner's assertion that the term "functional" allegedly is indefinite. The amendment is also supported, for example, at page 9, lines 11-16. Claims 21, 27 and 96 have been amended to clarify that the heavy and light chain variable region sequences each have 3 CDRs, first, second and third complementarity determining regions (CDR1, CDR2 and CDR3), and that CDR3 of heavy chain variable region comprises amino acids 99-108 of SEQ ID NO:5. Dependent claims 28, 29 and 35 have been similarly amended. The amendment is also supported, for example, at page 20, lines 7-10. Thus, the amendments do not add new matter and entry thereof is requested.

Regarding the Priority Claim

Applicants respectfully disagree with the conclusion that claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 do not properly benefit to the earlier filing dates of the priority applications under 35 U.S.C. §§119 or 120. Applicants also disagree that claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 contain new matter.

In particular, a claim for the benefit of an earlier filing date under 35 U.S.C. §§120 and 119 the application must name an inventor or inventors named in the prior application, a specific reference must be made to the prior application, the application must be filed prior to abandonment or termination of proceedings of the prior application, and the invention disclosed complies with the first paragraph of 35 U.S.C. §112. Here, the above-identified application has an inventor named in the prior application, namely PCT application PCT/IB2004/004453 filed November 12, 2004, makes a specific reference to the prior application, which designated the US, and was filed prior to abandonment or termination of proceedings of the prior application. Furthermore, prior application PCT/IB2004/004453, is identical to the above-identified application and therefore complies with 35 U.S.C. §112, first

paragraph. Consequently, the above-identified application properly claims and is fully entitled to the benefit of priority of application PCT/IB2004/004453 filed November 12, 2004, under 35 U.S.C. §120.

In terms of claiming priority to a provisional application under 35 U.S.C. §119, the application must be filed not later than 12 months after the date the provisional application was filed and a specific reference must be made to the provisional. Here, PCT application PCT/IB2004/004453 was filed November 12, 2004, which is not later than 12 months from the November 12, 2003, filing date of provisional application no. 60/519,550, and the above-identified application makes a specific reference to the priority provisional application. Furthermore, the priority provisional application is essentially identical to application PCT/IB2004/004453 and supports claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph. Consequently, the above-identified application properly claims and is fully entitled to the benefit of priority of provisional application no. 60/519,550, filed November 12, 2003, under 35 U.S.C. §119.

I. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, second paragraph as allegedly indefinite is respectfully traversed. Allegedly the claims are indefinite in the recitation of "functional fragment."

Claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are clear and definite. In this regard, as previously pointed out independent claims 21, 27 and 96 recite that the antibody or "functional fragment thereof specifically binds to an epitope of an antigen …." Thus, the skilled artisan would know that the recited function is binding. Accordingly, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are clear and definite and the rejection under 35 U.S.C. §112, second paragraph is improper.

Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 have been amended as suggested by the Examiner to recite "antigen-binding" fragment. In view of the amendment, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are clear and definite and the rejection under 35 U.S.C. §112, second paragraph.

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, second paragraph as allegedly indefinite is respectfully traversed. Allegedly the claims are indefinite in the recitation of "said epitope" as set forth in the Action at pages 16-17.

The meaning of the term "said epitope" in claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 is clear and definite to one of skill in the art. In particular, the first instance of a noun used in a claim is typically preceded by the indefinite article "a" or "an," such as "an" epitope. For reference to the same noun in second and subsequent instances the term is conventionally preceeded by the terms "the" or "said," such as "said" epitope. Here, in claims 21, 27 and 96, the first instance of "epitope" in lines 6, 4 and 6, respectively, are all preceded by the term "an" and the second instance of the term "epitope" in lines 11, 10 and 11, respectively, are all preceded by the term "said." Thus, the second instance of "said epitope" in claims 21, 27 and 96 refers to the epitope referred to in the first instance in claims 21, 27 and 96, namely "an epitope," and therefore the "epitope" in both instances is the same and adequate antecedent basis is provided. Consequently, the claimed antibodies and antigen binding fragments bind to the same epitope that NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 specifically binds, regardless of whether or not the recited cell lines express other epitopes. Accordingly, as claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are directed to antibodies and antigen binding fragments that specifically bind to the epitope that NORM-2 antibody specifically binds, they are clear and definite under 35 U.S.C. §112, second paragraph, and the rejection must be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description is respectfully traversed. According to the Patent Office, allegedly the skilled artisan would not be reasonably apprised that Applicants had possession of the claimed invention.

Applicants first respectfully reiterate that the "Guidelines for Examination of Patent Applications...." cited in the Action at page 4 are merely that, simply guidelines. The "Guidelines" are not statutory nor judicial authority; moreover, the guidelines are not promulgated as regulations. Consequently, Applicants will refrain from addressing the Examiner's continued reliance upon the "Guidelines" and any grounds for rejection based

upon the aforementioned "Guidelines" as they are not competent statutory, judicial or regulatory authority.

Applicants also wish to respond to several inaccurate statements in the Office Action. In particular, as to the assertion in the Office Action at page 5 that the amended claims "do not require that the antibodies bind to any particular antigen," the claims require that the antibodies and antigen binding fragments "bind to an epitope of antigen expressed by at least one of" five recited cell lines, wherein the "NORM-2 antibody produced by a cell line deposited as DSM ACC2626 specifically binds to said epitope of the antigen expressed by at least one of" the five recited cell lines. Thus, the claimed antibodies and antigen binding fragments bind to the same epitope to which the NORM-2 antibody produced by the cell line deposited as DSM ACC2626 binds. Consequently, the claimed antibodies and antigen binding fragments are required to bind 1) to a specific epitope of an antigen, and 2) to the same epitope as the NORM-2 antibody binds.

In addition, the claimed antibodies and antigen binding fragments include a heavy chain variable region with three CDRs, CDR1, CDR2 and CDR3, and a light chain variable region with three CDRs, CDR1, CDR2 and CDR3, and have been amended as such. Thus, all 3 CDRs, namely CDR1, CDR2 and CDR3, are present in each of the heavy and light chain variable region sequences. Furthermore, the amended claims recite that heavy chain variable region CDR3 comprises amino acids 99-108 of SEQ ID NO:5. Consequently, the grounds for rejection due to absence of in all 6 complementarity determining regions (CDRs), and that the claims do not indicate that amino acids 99-108 of SEQ ID NO:5 comprise CDR3 are moot.

Turning to the remaining ground for rejection, the Patent Office then states at page 6 that "the claims are not directed to antibodies that specifically bind to a well characterized antigen," but even if this were true this is not dispositive of the written description requirement for the claims under 35 U.S.C. §112, first paragraph. In fact, the notion that without the antigen sequence that antibodies and binding fragments are not adequately described as a matter of law, is not supported by any case law. Again, the claims are directed to antibodies and antigen binding fragments. In *Enzo Biochem, Inc v. Gen-Probe Inc.*, 323 F3d 956 (Fed. Cir. 2002), *Enzo II,* the court offered an example of a claim that the PTO would find in compliance with §112, first paragraph, defined by functional characteristics, namely "an isolated antibody capable of binding to antigen X....in light of the well defined structural characteristics of the five classes of antibody, the functional characteristics of

antibody binding, and the fact that the antibody technology is well developed and mature." Thus, under *Enzo II*, antibodies and binding fragments are adequately described under 35 U.S.C. §112, first paragraph solely in terms of functional characteristics since the structural characteristics of antibodies are well known and are coupled with the functional characteristic of binding. Consequently, the written description requirement with respect to a genus of antibodies and binding fragments can be satisfied, as it is here, given sufficient relevant identifying functional characteristics and a correlation between structure and function, even if the antigen has not been fully characterized.

In terms of sufficient relevant structural characteristics, as previously pointed out in the record, the claimed antibodies and binding fragments are defined structurally, with at least 80% sequence identity to heavy and light chain variable region sequences, SEQ ID NO:5 and 7, and wherein heavy chain CDR3 comprises amino acids 99-108 of SEQ ID NO:5. In terms of sufficient relevant functional characteristics, the claimed antibodies and binding fragments functionally bind to an epitope of an antigen to which the NORM-2 antibody binds. Furthermore, the epitope of the antigen to which the claimed antibodies and fragments bind is defined in terms of 1) expression by at least one of 5 particular cell lines; and 2) by binding to the same epitope as NORM-2 antibody produced by a cell line deposited as DSM ACC2626 specifically binds. Thus, in contrast to the facts in *Enzo Biochem, Inc v. Gen-Probe Inc.*, 296 F3d 1316 (Fed. Cir. 2002) the claimed antibodies and binding fragments are not defined "solely by its principal biological property."

In terms of structure correlating with function, as discussed in the record and in greater detail below, there was substantial knowledge concerning antibody structure correlating with function in the art at the time of the invention. Furthermore, the specification exemplifies representative antibody heavy and light chain variable region sequences, SEQ ID NOs:5 and 7, and the predicted location of CDRs and FRs. Thus, in view of the well understood correlation of structure and function and the guidance in the specification, as corroborated by the accompanying Declaration under 37 C.F.R. §1.132 by Dr. Vollmers, one of skill in the art could envision a number of antibodies and fragments having binding activity. Consequently, one of skill in the art would know of a number of antibodies and fragments having binding activity without needing to know the sequence of the antigen to which the claimed antibodies and fragments bind. To satisfy written description for the claimed antibodies and binding fragments under 35 U.S.C. §112, first paragraph therefore does not require one of skill in the art to know anything more about the

antigen than what is recited in the claims. As discussed in greater detail below, the claimed antibodies and binding fragments meet the description standard set forth by the court in *Enzo II*, as corroborated by the more recent decision in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005).

A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence…..Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science….the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005), emphasis added. In sum, an adequate written description is a factual inquiry measured by one of ordinary skill in the art that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

There is no requirement for an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Furthermore, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, an actual reduction to practice or disclosure of specific examples of antibodies or binding fragments within the scope of the claims is clearly not required to satisfy written description under 35 U.S.C. §112, first paragraph.

Here, the claims comply with the written description requirement under 35 U.S.C. §112, first paragraph. First, as discussed above and in the record, the claimed antibodies and antigen binding fragments are defined structurally, with at least 80% sequence identity to heavy and light chain variable region sequences, SEQ ID NO:5 and 7. Furthermore, the claimed antibodies and functional fragments include a heavy chain variable region with all amino acids (99-108) of predicted CDR3 of SEQ ID NO:5. Moreover, members of an antibody genus that bind to a common epitope typically share sequence homology, such as in CDR3 of heavy chain variable region. Thus, antibodies that bind to the same epitope as NORM-2 antibody will inherently share sequence homology with SEQ ID NO:5 and/or SEQ ID NO:7. The claimed antibodies and antigen binding fragments are also characterized functionally, by binding to an epitope of an antigen to which the NORM-2 antibody binds. Consequently, the claimed antibodies and antigen binding fragments share 1) a common structural relationship with SEQ ID NO:5 and/or SEQ ID NO:7 (sequence identity); and 2) a common functional relationship with NORM-2 antibody, namely binding to the same epitope as NORM-2 antibody binds.

Second, the claimed antibodies and functional fragments bind to an epitope of an antigen that NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 binds, and the antigen is expressed by at least one of 5 specifically defined cell lines. Thus, the epitope of the polypeptide is also defined in terms of 1) expression by at least one of 5 defined human cell lines; and 2) binding to NORM-2 antibody produced by a cell line deposited as DSM ACC 2626. Thus, one of skill in the art would know, without having to know more about the identity of the epitope or antigen, antibodies and functional fragments within the scope of the claims. For example, competition binding is a simple and routine technique known in the art at the time of the invention to verify that a given antibody or fragment binds to an antigen expressed by a cell, and an antibody or fragment that competes for NORM-2 binding to an antigen expressed by at least one of the specifically recited cell lines would be within the scope of the claims. Consequently, one of skill in the art needs no more information about the epitope or antigen identity in order to know antibodies and binding fragments within the scope of the claims.

As already pointed out in the record, the knowledge and skill in the art in terms of antibody structure correlating with function at the time of the invention was high. Namely, the role of antibody heavy and light chain variable regions, including CDRs and FRs in antigen binding, was well understood by the skilled artisan at the time of the invention. The

specification also discloses the role of antibody heavy and light chain variable regions in antigen binding, the variable light and heavy chain region sequences (e.g., SEQ ID NOs:5 and 7), as well as the predicted sequences and positions of all CDRs and therefore also the location of the FRs. Consequently, the level of knowledge and skill in the art with respect to antibody structure (CDRs, FRs, D- and J-regions, etc.) correlating with function was high, and the predicted locations and amino acid sequences of all CDRs and FRs of SEQ ID NOs:5 and 7 that contribute to antigen binding would therefore be known to one of skill in the art.

Because the knowledge and skill in the art in terms of antibody structure correlating with function was high and the predicted location and sequences of CDRs and FRs in SEQ ID NOs:5 and 7 that contribute to antigen binding are disclosed, the skilled artisan would also have known residues in SEQ ID NOs:5 and 7 amenable to substitution. For example, in view of the understanding of the role of CDRs and FRs in antigen binding, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, insertion or a deletion, for example, outside of a CDR or FR region of in SEQ ID NOs:5 and 7 would be unlikely to destroy antigen binding activity. Furthermore, because of the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention one skilled in the art could predict with a high degree of confidence many substitutions of SEQ ID NOs:5 and 7 that would not destroy binding activity. Moreover, the Declaration under 37 C.F.R. §1.132 submitted herewith discussed in detail below and previously submitted Exhibits A-D (filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009, respectively) evidence that substitutions and deletions/insertions of amino acids within antibody CDRs (i.e., CDR1, CDR2 or CDR3) and FRs would be known to one of skill in the art and can be well tolerated.

The facts underlying the claimed antibodies and binding fragments are therefore analogous to the facts underlying *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), in which the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description for claims directed to a genus of such proteins since the single disclosed protein embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patent claims satisfied the written description requirement, as articulated in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description

for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents-in-issue in *Invitrogen*, which did not recite a particular amount of homology or identity to a reference sequence, satisfied the written description requirement even though there was only a single disclosed embodiment in the specification. In view of *Invitrogen*, a single embodiment provides an adequate written description of a genus of proteins where as here there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, given the substantial understanding of antibody structure correlating with function at the time of the invention, that the specification discloses heavy and light chain variable region sequences including predicted positions and sequences of all CDRs and FRs, all sequences that mediate antigen binding would be known to one of skill in the art and therefore residues and regions amenable to substitution, insertion or deletion would also be known. The claimed antibodies and functional fragments also share structural (sequence homology) characteristics with reference sequences (SEQ ID NOs:5 and 7) and functional characteristics (bind to the epitope to which NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 specifically binds). Consequently, the underlying facts of the claims under consideration closely parallel the facts in the *Invitrogen* decision.

Additionally, the accompanying Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers verifies that the claims are adequately described under 35 U.S.C. §112, first paragraph. Dr. Vollmers provides objective facts, and conclusions based upon the objective facts, in the accompanying Declaration.

In terms of antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:5 and a light chain variable region sequence at least 75% identical to SEQ ID NO:7, Dr. Vollmers declares and states at paragraphs 6 to 15 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically

bind to a polypeptide expressed by at least one of the recited cell lines, and (i) that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:5, and comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:7; (ii) that comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:5, and comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:7; (iii) that comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:5, and comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:7; (iv) that comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:5, and comprise a light chain variable region sequence at least 90% identical to SEQ ID NO:7; or (v) that comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:5, and comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:7.

Dr. Vollmers' conclusions are based upon the following objective facts: The specification discloses the heavy chain variable region amino acid sequence, SEQ ID NO:5, and light chain variable region amino acid sequence, SEQ ID NO:7. The specification discloses that heavy and light chain variable region sequences SEQ ID NOs:5 and 7 are derived from a human antibody (Example 1). The specification also discloses the predicted sequence of all three CDRs in both variable region sequences (see, for example, Figures 9 and 10, page 3, lines 9-12 and 15-19). Dr. Vollmers therefore concludes that the skilled artisan would know the sequence and the predicted locations of the three CDRs in heavy and light chain variable regions, SEQ ID NOs:5 and 7.

Dr. Vollmers' furthermore declares that as the predicted locations of the three CDRs in SEQ ID NOs:5 and 7 would be known to the skilled artisan, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:5 and 7, as well as the D- and J-regions in SEQ ID NOs:5 and 7. Dr. Vollmers therefore declares that the skilled artisan would know the sequence and location of amino acid residues of SEQ ID NOs:5 and 7 that contribute to antigen binding.

Dr. Vollmers declares that the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art, the specification discloses the function of antibody heavy and light chain variable (e.g., CDR and FR) and constant regions (page 19, line 11, to page 20, line 15). The role of variable region sequences, including CDRs in

antigen binding was known in the art at the time of the invention (see, for example, Immunology, Goldsby, R.A., 5th ed. W.H. Freeman, 2002).

Dr. Vollmers also declares that because the amino acids of heavy and light chain variable region sequences SEQ ID NOs:5 and 7 that contribute to antigen binding would be known to one of skill in the art in view of the specification and the high level of knowledge and skill in the art concerning antibody structure and function, the skilled artisan would have known a number of antibodies and functional fragments with amino acid residues of SEQ ID NOs:5 and 7 that could be substituted (i.e., would likely not destroy binding activity). Consequently, the skill artisan would envision heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7 that would have at least partial binding activity.

Dr. Vollmers illustrates the foregoing by way of the example of an amino acid substitution. In brief, an amino acid substitution such as a non-conservative or conservative substitution outside a CDR or FR region of SEQ ID NOs:5 or 7 would likely not destroy binding activity of an antibody, and conservative substitutions within a CDR or FR region of SEQ ID NOs:5 or 7 would also likely not destroy binding activity of an antibody or antigen binding fragment. Dr. Vollmers thus declares that the skilled artisan would know of a number of antibodies and antigen binding fragments comprising SEQ ID NO:5 or 7 with non-conservative or conservative substitutions located outside of a CDR or FR of SEQ ID NO:5 or 7, or conservative substitutions within a CDR or FR of SEQ ID NO:5 or 7, that likely retain at least partial binding activity (paragraph 10).

Dr. Vollmers points out that typically about half of the amino acids in a given heavy or light chain variable region sequence is not within one of the three CDRs. Dr. Vollmers concludes that because there are a large number of amino acids outside of the CDRs, the skilled artisan would envision a number of residues outside of CDRs that could be substituted and likely retain at least partial binding activity. Thus, Dr. Vollmers declares that the skilled artisan would readily envision antibodies and antigen binding fragments with heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7, that would retain at least partial binding activity without actually having to verify that the variant has at least partial binding activity (paragraph 11).

Dr. Vollmers further declares that not only would the skilled artisan envision antibodies and antigen binding fragments with heavy chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5, and light chain variable region sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7, that retain at least partial binding activity, but would also know of nonfunctional variants. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to confer fine binding specificity, and therefore that a large number of non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen specificity. Dr. Vollmers therefore concludes that the skilled artisan would also know of variants of SEQ ID NOs:5 and 7 with sufficient substitutions, insertions or deletions such that the antibody or functional fragment would be unlikely to have binding activity (paragraph 12).

Dr. Vollmers moreover declares that the ability of the skilled artisan to envision sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:5 and sequences with 75% or more (e.g., 80%, 85%, 90%, 95%, etc.) identity to SEQ ID NO:7 that would retain at least partial binding activity is further evidenced by the fact that humanizing antibodies was known at the time of the invention (see, for example, U.S. Patent No. 6,180,370). In particular, Dr. Vollmers points out that grafting non-human CDRs to human framework sequences to form an antigen binding antibody was well established at the time of the invention. Dr. Vollmers concludes that because all CDRs of a given variable region sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant antibody, the skilled artisan would readily envision antibodies and antigen binding fragments could comprise CDRs of one species and fragments of another without destruction of antigen binding activity that comprise heavy chain variable region sequences with 75% or more identity to SEQ ID NO:5, and light chain variable region sequences with 75% or more identity to SEQ ID NO:7. Moreover, Dr. Vollmers concludes that given that humanized antibodies retain binding and that variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, variants can be substantially non-identical to SEQ ID NOs:5 and 7 outside of the CDRs while retaining binding activity. Dr. Vollmers thus concludes that the skilled artisan would readily envision a number of antibodies and antigen binding fragments that vary in positions outside of the CDRs of SEQ ID NOs:5 and 7 that retain at least partial binding activity (paragraph 13).

To illustrate that substitutions within CDRs are tolerated, Dr Vollmers refers to Kipriyanov *et al.* (Protein Engineering 10:445 (1997), previously submitted as Exhibit A (filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009) whom report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on binding affinity. Thus, Exhibit A corroborates that the skill artisan would know that a substitution of a light or heavy chain variable region CDR residue are tolerated and would not necessarily destroy binding activity (paragraph 14).

To illustrate that substitutions within FRs can generally be tolerated, Dr. Vollmers refers to Holmes *et al.* (J. Immunol. 167:296 (2001), previously submitted as Exhibit B, filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009), whom report that several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Dr. Vollmers' concludes that antibodies and antigen binding fragments with a substitution of a heavy or light chain variable region FR residue are tolerated and would not destroy binding activity (paragraph 15).

Concerning antibodies and functional fragments that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:5 and a light chain variable region sequence at least 75% identical to SEQ ID NO:7, wherein the heavy or light chain variable region sequence has an insertion or deletion of one amino acid residue, Dr. Vollmers declares and states at paragraphs 16 to 19 of the Declaration that:

One skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically bind to a polypeptide expressed by at least one of the recited cell lines and that comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:5 and a light chain variable region sequence at least 75% identical to SEQ ID NO:7, wherein the heavy or light chain variable region sequence has an insertion or deletion of an amino acid residue (paragraph 16).

Dr. Vollmers' conclusions are based upon the following objective facts: again, the sequence of amino acid residues of heavy and light chain variable region sequences SEQ ID NOs:5 and 7 and corresponding CDRs, FRs, etc., that contribute to antigen binding would be known, and the level of knowledge and skill in the art concerning antibody structure and

function was high. Consequently, the skilled artisan would have known antibodies and fragments with substitutions of SEQ ID NOs:5 and 7 that would not destroy binding activity, and therefore would envision variable region sequences with 75% or more identity to SEQ ID NO:5 and 7 (e.g., 80%, 85%, 90%, 95%, etc.) with at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:5 or 7 would also likely not destroy binding activity of an antibody (paragraph 18).

To corroborate the foregoing conclusions concerning insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, Dr. Vollmers points out that such alterations occur during antibody affinity maturation, and refers to Wilson *et al.* (J. Exp. Med. 187:59 (1998) previously submitted as Exhibit C, filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009), whom report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation. Dr. Vollmers therefore concludes that the skilled artisan would know with a high degree of confidence that an antibody or antigen binding fragment comprising SEQ ID NO:5 or 7 with an amino acid insertion or deletion within or outside of a CDR, would very likely retain at least partial binding activity.

To further corroborate Dr. Vollmers' conclusions that antibodies and antigen binding fragments with a heavy or light and chain variable region sequence insertion or deletion can be tolerated, even within a CDRs, he refers to Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002), previously submitted as Exhibit D, filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009), whom report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibits C and D corroborate that antibodies and antigen binding fragments that comprise a heavy or light chain variable region sequence insertion or deletion, even within a CDR, can be tolerated (paragraph 19).

In sum, given the totality of: guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the heavy and light chain variable region sequences (SEQ ID NOs:5 and 7) and the CDRs and FRs that confer binding, and as also corroborated by the Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers submitted herewith and previously submitted Exhibits A-D, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:5 and 7 having binding activity, the claims meet

the written description standard articulated by the court in *Invitrogen*. Further in view of the substantial understanding of antibody sequence structure and correlation with function at the time of the invention, the significant degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:5 and 7, and that the claimed antibodies and fragments bind to a single identical epitope, namely the epitope to which the NORM-2 antibody binds, and will also necessarily have sequence homology with SEQ ID NOs:5 or 7, the facts of the claims under consideration meet the standard meet the standard set forth by the court for written description in *Invitrogen*. Consequently, the claims are adequately described under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description is respectfully traversed. According to the Patent Office, the recitation of "and that includes amino acids 99-108 of SEQ ID NO:5" in claim 21, and the recitation of "wherein the antibody or functional fragment thereof specifically binds to an epitope of an antigen expressed by...." one of five deposited cell lines "...wherein NORM-2 antibody specifically binds to said epitope of the antigen...." in claims 21, 27 and 96 are allegedly new matter.

In terms of the recitation of "amino acids 99-108 of SEQ ID NO:5," the originally filed specification discloses and the claims recite that polypeptides can be "substantially identical" to a reference amino acid sequence (e.g., SEQ ID NO:5 or 7) (see for example, page 14, lines 4-14, and claim 42). The specification discloses that substantially identical means polypeptides or nucleic acids exhibiting 80% or more, to a reference sequence, which can even be 100% identical to a reference sequence. (page 14, lines 4-10) In this regard, the recitation of amino acids 99-108 of SEQ ID NO:5 in claim 27 means that the heavy chain variable region sequence is "100% identical" to this region. The specification also discloses that the length of comparison for purposes of the percent identity will generally be at least 3, 4, 5, or more amino acids, in particular, for example, "10" contiguous amino acids. (page 10, lines 1-5; and page 14, lines 10-14). In this regard, there are "10" contiguous amino acids in amino acids 99-108 of SEQ ID NO:5 recited in claim 27. Thus, clearly the specification supports the recited language of percent identity of SEQ ID NO:5 and 7 in combination with the "10" contiguous amino acids of the specified sequence region. In addition, as correctly noted by the Examiner, the specification discloses the predicted locations of the CDRs of SEQ ID NO:5 and 7, that the invention includes polypeptides (e.g., antibodies and fragments

thereof, page 3, lines 12-14) with one or more CDRs of SEQ ID NO:5 and/or 7 (see, e.g., page 3, lines 1-12; and page 10, lines 5-12) and that such sequences may have less than all of the amino acids of SEQ ID NO:5 or 7 (e.g., 3, 4, 5 etc.), or be the entire amino acid sequence SEQ ID NO:5 and 7, and which may include one or more of the CDRs of the V_H or V_L regions of the NORM-2 antibody (page 10, lines 1-7), such as amino acids 99-108 of SEQ ID NO:5 (page 10, lines 5-11). Furthermore, antibodies and functional fragments thereof that recite only one or more CDRs of SEQ ID NOs:5 or 7 have less than 100% sequence identity to SEQ ID NOs:5 or 7, and therefore such antibodies and functional fragments with one or more CDRs of SEQ ID NOs:5 or 7 are within the meaning of "substantially identical." Thus, clearly the specification supports the recited language of percent identity of the heavy chain variable region in the context of the "10" contiguous amino acids "100%" identical to the specified CDR of SEQ ID NO:5, namely amino acids "99-108 of SEQ ID NO:5."

In terms of the recitation of the "antibody or functional fragment thereof specifically binds to an epitope of an antigen expressed by...." one of five deposited cell lines "...wherein NORM-2 antibody specifically binds to said epitope of the antigen...." in claims 21, 27 and 96, Applicants respectfully point out that in view of the response to the rejection under 35 U.S.C. §112, second paragraph discussed above, that the claims do not recite different epitopes. Rather, the "epitope" to which the claimed antibodies and antigen binding fragments bind is the same "epitope" that NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 specifically binds, regardless of whether or not the recited cell lines express other different epitopes. Support for the claim language is previously described in the Response filed June 4, 2009. Accordingly, as claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are directed to antibodies and antigen binding fragments that specifically bind to the epitope that NORM-2 antibody specifically binds, and do not bind to different epitopes, they are clear and definite under 35 U.S.C. §112, second paragraph, and the rejection must be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent Office, allegedly it is unclear if the cell lines recited in the claims are publicly available. In terms of claim 47, it allegedly is unclear if the NORM-2 cell line is available.

As a first issue, a deposit is not required for publicly available materials. In this regard, previously submitted Exhibit E (filed January 26 and June 4, 2009, in support of the Responses to Office Actions mailed on July 25, 2008, and May 1, 2009) evidences that Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cell lines are available to the public from DSMZ. Exhibit E included the relevant pages from the DSMZ catalog and a material transfer agreement for ordering these cell lines from DSMZ. Thus, Exhibit E is sufficient evidence demonstrating that each of the cell lines are available to the public. Consequently, as these cells are publicly available, there is no need for Applicants to independently provide deposit information and the ground for rejection under 35 U.S.C. §112, first paragraph must be withdrawn.

In terms of availability of the cell line deposited as DSM ACC2626, Applicants respectfully point out that the cell line deposited as DSM ACC2626 is not required to enable the claims under 35 U.S.C. §112, first paragraph. As pointed out in the record, the specification discloses heavy and light chain variable regions of NORM-2, SEQ ID NOs:5 and 7. Thus, one of skill in the art could produce an antibody or antigen binding fragment comprising SEQ ID NOs:5 and 7 without undue experimentation. Notwithstanding the foregoing, Applicants affirm that the deposit of DSM ACC2626 will be made available to the public in accordance with 37 CFR 1.801-1.809 upon grant of a patent. Consequently, this ground for rejection under 35 U.S.C. §112, first paragraph is moot.

The rejection of claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. Allegedly it would require undue experimentation to make and use the claimed antibodies and functional fragment, as set forth in the Office Action at pages 10-12.

Applicants first respectfully point out that the claims have been amended to clarify that, among other things, the heavy and light chain variable regions each include three CDRs, CDR1, CDR2 and CDR3. Thus, as all 6 CDRs are present in the claimed antibodies and antigen binding fragments, the ground for rejection due to substitutions and variants having less than the full complement of 6 CDRs is moot.

Applicants also respectfully point out that the claimed antibodies and antigen binding fragments bind to the epitope to which the NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 specifically binds. Thus, as the antibodies and antigen binding fragments all bind to the same epitope, the grounds for rejection due to binding to different epitopes on different antigens (page 12, first paragraph) is moot.

In terms of the remaining grounds for rejection, it appears that the Examiner believes satisfying the enablement requirement under 35 U.S.C. §112, first paragraph requires that antibody variants must be disclosed (see, at page 11, first and second paragraphs), or that one of skill in the art would need to "predict" in advance or would need to know beforehand which CDRs or other regions could be altered substituted while maintaining antigen binding function (see, e.g., page 11, last paragraph). However, specific examples are not required to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, and furthermore, one of skill in the art could make and use the claimed antibodies and antigen binding fragments including variants without any need to predict in advance or know beforehand which sequence regions could be altered or substituted.

As previously pointed out, the proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* 858 F.2d 731, 737 (Fed. Cir. 1988) Here, in view of the guidance in the specification and knowledge and skill in the art at the time of the invention variants of antibodies and antigen binding fragments having the requisite activity could be made and used without undue experimentation using routine methods disclosed in the specification or known in the art at the time of the invention. Consequently, analogous to *Wands*, where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to make and identify variant antibodies and antigen binding fragments that bind to an epitope of an antigen expressed by at least one of the recited cell lines, to which epitope NORM-2 antibody binds, given that 1) producing antibody variants and fragments was routine in the art at the time of the invention; and 2) binding assays are disclosed in the specification or were known in the art at the time of the invention.

Thus, there is no need for the skilled artisan to "predict" in advance or need to know beforehand antibody or binding fragment variants that bind to the epitope of the antigen to which NORM-2 antibody binds because making antibodies and fragments and identifying those that bind, induce apoptosis or inhibit cell proliferation would not require undue experimentation at the time of the invention.

Consequently, the statements in the Office Action that purportedly support a lack of enablement, namely that allegedly one of skill in the art "cannot predict" or that "it cannot be known beforehand" or allegedly that it would be undue experimentation "to determine which CDRs could predictably be altered or substituted" are irrelevant since there is no need to predict or know beforehand the effect of any amino acid change in order to obtain antibodies and antigen binding fragments having the recited activities without undue experimentation.

In support of Applicants position, claims directed to a genus of antibodies where no antibody has ever been produced are routinely granted by the Patent Office. Thus, if claims directed to a genus of antibodies have been granted where no antibody has even been made and therefore where no antibody sequences are even known, surely knowledge of antibody sequence or predicting the effects of particular amino acid variations on binding is not required to satisfy the enablement requirement under 35 U.S.C. §112. Consequently, clearly enablement under 35 U.S.C. §112 does not require knowledge of antibody sequence or predicting the effects of particular sequence variations on antibody binding or activity. Thus, the repeated statements by the Patent Office that one would have to predict or know beforehand the effect of changes in antibody sequence on binding or other activities clearly indicates that the Patent Office is applying an incorrect enablement standard to the claims.

Furthermore, the Patent Office cannot insist that the specification enable the claims by a particular methodology, namely the requirement of predicting or knowing in advance which variants that bind or have another activity. In this regard, there is no authority requiring Applicant to demonstrate enablement by a particular methodology selected by the Patent Office to the exclusion of others. Consequently, the Patent Office cannot demand that Applicant demonstrate enablement by a particular methodology under 35 U.S.C. §112, first paragraph.

Here, in view of the fact that knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was high at the time of the invention, and that antibodies having binding and other activities could be readily identified without undue experimentation at the time of the invention, one of skill in the art could readily make

antibody variants having the requisite binding and other activities without undue experimentation. Consequently, there is no need to predict or know in advance which variants that bind or have another activity in order to obtain variant antibodies without undue experimentation.

First, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 23, line 14, to page 26, line 19). Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and antigen binding fragments without undue experimentation.

Second, methods of identifying antibodies and fragments that bind antigen or have other activities without undue experimentation are also taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 44, line 9, to page 45, line 19; and page 49, line 10, to page 54, line 14). Thus, antibodies and binding fragments that bind to an epitope of an antigen expressed by at least one of the recited cells, to which epitope NORM-2 antibody binds, as well as antibodies that inhibit cell proliferation and induce apoptosis, could be identified without undue experimentation at the time of the invention.

For example, if one skilled in the art wanted to produce antibodies or antigen binding fragments that specifically bind to an epitope of an antigen expressed by at least one of the recited cells, to which epitope NORM-2 antibody also binds, the skilled artisan could simply introduce mutations in a light and/or heavy chain variable region sequence (SEQ ID NOs:5 or 7) and then verify those that bind to the epitope to which NORM-2 antibody binds, for example, by a competition binding assay with NORM-2 antibody for binding to one or more of the recited cells. A particular example of the routine nature of methods of producing and identifying variant antibodies having binding activity at the time of the invention is submitted herewith as Exhibit G (Boder *et al.*, Proc. Nat'l Acad. Sci. USA 97:10701 (2000)). The authors of Exhibit G describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Notably, the authors state "[t]he relative ease with which extremely high affinity has been attained in this study." (page 10705, first column, last full paragraph)

Consequently, in view of the fact that functional variants with improved affinity could be made "with relative ease" at the time of the invention, one of skill in the art clearly would have been able to produce variant antibodies and fragments having binding affinity without any need to predict in advance or know the effect of any amino acid variation without undue experimentation at the time of the invention.

In sum, analogous to *In re Wands* where the court held that identifying hybridomas that have a particular binding characteristic did not require undue experimentation, making and identifying antibodies and antigen binding fragments that bind to the epitope to which NORM-2 antibody binds would not require undue experimentation, given that 1) producing antibodies and fragments was routine in the art at the time of the invention; and 2) routine cell binding, antibody competition and cell proliferation/apoptosis assays are disclosed in the specification or were known in the art at the time of the invention. Consequently, contrary to the statements in the Office Action where it is alleged that one skilled in the art would have to "predict" or "know beforehand" the effect of sequence changes on binding, inhibition of cell proliferation or induce apoptosis, there is no need for the skilled artisan to "predict" or "know beforehand" variants or fragments that bind to the recited polypeptide, inhibit cell proliferation or induce apoptosis, in order to obtain variants and antigen binding fragments because making and identifying antibodies and antigen fragments having the requisite binding, inhibition of cell proliferation or induction of apoptosis was routine at the time of the invention.

Thus, in view of the high level of knowledge and skill in the art at the time of the invention clearly the skilled artisan could make antibodies and fragments and identify those that bind in view of the guidance in the specification and knowledge in the art at the time of the invention without undue experimentation. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

To further corroborate that one of skill in the art could produce antibodies and antigen binding fragments having binding and other activities without undue experimentation at the time of the invention, submitted herewith is a Declaration under 37 C.F.R. §1.132, executed by Dr. Peter Vollmers. As stated in the Declaration, Dr. Vollmers, based upon objective facts, concludes that one of skill in the art, in view of the guidance in the specification and knowledge in the art at the time of the invention, could have produced antibodies and functional fragments having binding and other activities without undue experimentation (Paragraph 20). The facts and Dr. Vollmers' conclusions therefrom are summarized in the

Declaration, Paragraphs 20-24. Accordingly, the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers corroborates that one of skill in the art could produce antibodies and antigen binding fragments having binding and other activities without undue experimentation at the time of the invention.

In sum, given the fact that one skilled in the art could obtain variant antibodies and antigen binding fragments that bind to an epitope of an antigen expressed by at least one the recited cells to which NORM-2 antibody produced by a cell line deposited as DSM ACC 2626 also binds without undue experimentation at the time of the invention, one skilled in the art would not need to predict in advance or need to know beforehand sequence regions that could be altered or substituted. In addition, the Patent Office cannot properly require Applicants to show enablement by a particular methodology specified by the Patent Office, i.e., to know or be able to predict in advance variants to satisfy 35 U.S.C. §112, first paragraph. Here, one skilled in the art is not required to predict or know in advance the effect of any change in order to obtain antibodies and fragments that bind without undue experimentation, as held by the court in *Wands*, and corroborated by Exhibit G and the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

In view of the foregoing, the skilled artisan could make antibody variants and antigen binding fragments as claimed without undue experimentation. Consequently, claims 21 to 23, 27 to 32, 35, 47 and 89 to 96 are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. §102

The rejection of claims 21, 27, 30, 31, 32, 47 and 95 under 35 U.S.C. §102(b), as allegedly anticipated by Immunobiology 5 (Janeway et al. pp 96-7 (2001), as evidenced by Kettunen (C. Gen. Cyto. 149:98 (2004)) is respectfully traversed. According to the Patent Office, allegedly the Immunobiology reference describes each and every element of claims 21, 27, 30, 31, 32, 47 and 95.

Claims 21, 27, 30, 31, 32, 47 and 95 are neither taught nor suggested by the cited references. In particular, the amended claims recite, *inter alia*, an "antigen-binding" fragment. Furthermore, the amended claims recited that the antibody comprises a heavy chain variable region with at least 80% identity to SEQ ID NO:5 and a light chain variable

region with at least 80% identical to SEQ ID NO:7. In contrast, neither of the cited references alone, or in combination, teach or suggest an antibody or antigen binding fragment thereof comprising a heavy chain variable region with at least 80% identity to SEQ ID NO:5 and a light chain variable region with at least 80% identical to SEQ ID NO:7, and that binds to an epitope of an antigen expressed by at least one of Colo-699 (DSMZ Accession Number ACC 196), CACO-2 (DSMZ Accession Number ACC169, ATCC Accession Number HTB-37), 23132/87 (DSMZ Accession Number ACC 201), DU-145 (DSMZ Accession Number ACC 261, ATCC Accession Number HTB-81), and BM 1604 (DSMZ Accession Number ACC 298) cells. Consequently, each and every element of claims 21, 27, 30, 31, 32, 47 and 95 are neither taught nor suggested by Immunobiology 5 (Janeway et al. pp 96-7 (2001) alone, or in combination with Kettunen (C. Gen. Cyto. 149:98 (2004)). Accordingly, claims 21, 27, 30, 31, 32, 47 and 95 are not anticipated under 35 U.S.C. §102(b) in view of Immunobiology 5 (Janeway et al. pp 96-7 (2001), as evidenced by Kettunen (C. Gen. Cyto. 149:98 (2004)) and as such, the rejection must be withdrawn.

The rejection of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 under 35 U.S.C. §102(b), as allegedly anticipated by Vollmers et al. (Cell 40:547 (1985)) is respectfully traversed. According to the Patent Office, allegedly Vollmers et al. describe each and every element of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96.

Claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 are neither taught nor suggested by the cited reference. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amend claims upon entry of this response.

Applicants respectfully reiterate that a reference cited under 35 U.S.C. §102 must have an enabling disclosure. However, claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 have also been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Consequently, the rejections are contradictory: if the claims lack enablement under 35 U.S.C. §112, then the claims cannot also be rejected under 35 U.S.C. §102 since Vollmers et al. must be an enabling disclosure in order to properly be cited against the claims; if, on the other hand the claims are rejected under 35 U.S.C. §102, then they must be enabled and then the claims cannot also be rejected under 35 U.S.C. §112 as lacking enablement. Applicants

therefore request withdrawal of either the rejection under 35 U.S.C. §112 or the rejection under 35 U.S.C. §102 as they cannot be maintained simultaneously.

As a second issue, Vollmers et al. fail to enable one of skill in the art at the time of the invention to make the claimed antibodies and antigen binding fragments without undue experimentation. At best, Vollmers et al. mention an antibody by the same name as disclosed in the specification, NORM-2. However, there is no sequence information for heavy or light chain variable region sequences. Furthermore, there is no deposit information for any antibody, let alone, NORM-2 antibody. Thus, one of skill in the art would have been unable to obtain any antibody without undue experimentation, let alone the antibody or antigen binding fragment of claims 21 to 23, 27 to 31, 35, 47 or 89 to 96. Consequently, Vollmers et al. cannot fairly be presumed to be operable with respect to claims 21 to 23, 27 to 31, 35, 47 and 89 to 96, and as such, the rejection under 35 U.S.C. §102(b) is clearly improper and must be withdrawn.

If the Examiner continues to believe that Vollmers et al. is operable, the Examiner has the burden of explaining in detail how one of skill in the art could have produced the claimed antibodies and antigen binding fragments in view of Vollmers et al. at the time of the invention. Furthermore, since Vollmers et al. is not an enabling disclosure of the claims and also fails to enable or meaningfully describe NORM-2 antibody the Examiner cannot fairly presume that NORM-2 antibody was available and therefore cannot properly cite Vollmers et al. under 35 U.S.C. §102. Moreover, given the fact that Vollmers et al. is not operable for the reasons articulated above and in the record, the presumption of operability is rebutted and the burden is squarely on the Patent Office to present evidence that the antibody was available in order to maintain the rejection under 35 U.S.C. §102. Since only unsubstantiated conclusions and no evidence of any kind indicating public availability of NORM-2 prior to November 12, 2003 has been provided the rejection of claims 21 to 23, 27 to 31, 35, 47 or 89 to 96 under 35 U.S.C. §102 in view of Vollmers et al. is improper. Accordingly, the rejection under 35 U.S.C. §102(b) in view of Vollmers et al. (Cell 40:547 (1985)) must be withdrawn.

The rejection of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96 under 35 U.S.C. §102(a), as allegedly anticipated by Brandlein et al. (Cancer Res. 63:7995 (2003)) is respectfully traversed. According to the Patent Office, allegedly the cited reference describes each and every element of claims 21 to 23, 27 to 31, 35, 47 and 89 to 96.

The subject application claims priority to provisional application no. 60/519,550, filed November 12, 2003. As discussed above, the originally filed priority provisional application is essentially identical to application PCT/IB2004/004453, and adequately supports claims 21 to 23, 27 to 31, 35, 47 and 89 to 96. Consequently, as the claims are adequately supported as of November 12, 2003, and the publication date of Brandlein et al. (Cancer Res. 63:7995 (2003)) as indicated on the first page is November 15, 2003, Brandlein et al. (Cancer Res. 63:7995 (2003)) is not prior art against claims 21 to 23, 27 to 31, 35, 47 and 89 to 96. Accordingly, the rejection under 35 U.S.C. §102(a) in view of Brandlein et al. (Cancer Res. 63:7995 (2003)) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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